REMARKS

The claims have been revised as suggested by the Examiner to meet the objections raised. New claims 18, 19 and 20 are in a similar form addressed to pharmaceutical compositions containing specific groups of compounds. New claims 21 - 41 are similar to claims 1 -20 but specify the use of a prodrug wherein the hydroxy group of claim 1 is replaced by group that is hydrolizable *in vivo*. Support for such claims is found at page 4 lines 24 - 28 of the specification. Support for new claims 42 and 43 is found in the Table on page 10 with respect to compound 1.. Support for new claims 44 and 45 is found at page 2 lines 14 and 15

Claims 10 and 14 have been amended into method of treatment claims so that the rejection under 35 USC 112 should now be moot.

Turning to the rejection under 35 USC 103, the applicant respectfully submits that the reasons for patentability over the cited art are clearly set out on pages 2 and 3 of the specification. The difference noted by the examiner between the compound of Woods reference (combretastatin A-4) and the compounds of the present invention are pointed out in the present application and the reasons why one skilled in the art would not be motivated to modify combretastatin A-4 are discussed in the present application starting at page 2 line 21. In particular the reasons why one would not seek to replace the B ring methoxy group of combretastain with the groups of the present application are set out at page 3 lines 11 to 14.

The Examiner's specific obviousness rejection is believed to be misconceived. It seems that she has conflated the disclosure of combretastatin A-4 (in which there is a 4'-methoxy group and a neighboring hydroxyl group) with the teaching of Woods et al. In which the hydroxy group of combretastatin A-4 is removed and the methoxy group is replaced by a small alkyl group..

These teachings do not point to the compounds of formula 1 of the present application nor to prodrugs of such compounds. In the compounds of the present invention, a 3'-hydroxy group is present, irrespective of the nature of the group in the 4' position. The compounds described by Woods as actually having been made and tested all lack such a hydroxy group. The hypothetical formula on page 710 says that a 3'-hydroxy is optional, but there is no disclosure of any compound in which it is in fact present so that there is no basis for the conclusion that Woods draws that such a group might be present.

The Woods data show that there is a considerable loss in potency when the 3' hydroxy group is eliminated and the 4'-methoxy replaced by, for example a methyl group. Thus in Table 1 it is shown that there is a 4-5 fold loss in in vitro activity and Table IV show losses of activity of 3.5-, 11.2-, 35.8- and 27-fold respectively against the four cell systems examined. Had such a loss in activity occurred in the compounds of the present invention, they would have little value as vascular damaging agents. In fact as shown by the data in the present application and the test data submitted herewith, the efficacy of the compounds of Examples 1 and 2 is good, even at a low dose.

The additional data set out in the test results submitted herewith show remarkable and

unobvious results relating to the activity of the compound of Exampk,e 2 of the present application. The data show the efficacy of this compound in Sarcoma S, a solid tumor, in CBA mice. Such sarcoma is resistant to prior art vascular damagiing agents such as combretastatin A-4 phosphate. The compounds of the presentinvention therefore possess surprising advantages over the prior art compounds.

So far as claims 5 - 9 are concerned, nothing in the teaching of WO92/16486 or WO99/35130 overcomes the basic defects of Woods as a prior art reference as discussed above. In any case, the mechanism of the conversion of phosphate prodrugs into active agents relies on an efficient enzymatic cleavage of the phosphate group. Thus the phosphate in question has to fit the enzyme active site in order for it to be cleaved. Although certain general principles relating to cleavage of phosphate groups are known, it cannot be predicted a priori that a particular phosphate group can be removed at a rate that competes with elimination of the prodrug by other means. In particular, the compounds of the present inventiondiffer from the prior art compounds in a region of the molecule adjacent to the phosphate group. Such differences could well result in less favorable interactions at the active site of the cleaving enzymes and therefore result in insufficient cleavage of the phosphate and so poor in vivo activity for the compound. The good results obtained using the compound of Example 2 (a phosphate prodrug) cannot be predicted. Even if, as is not conceded, it may be obvious to try phosphate prodrugs, in the present situation there can be no reasonable expectation that such trials will succeed.

In view of the foregoing, it is submitted that this application should be allowed and the Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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ANNEX

Test Result

**Enhanced Activity of Novel VTAs Against CA4P-resistant Tumours**

The round-cell sarcoma, SaS, grown as a syngeneic subcutaneous tumour in CBA mice, is highly resistant to combretastatin A4 phosphate (Parkins CS, Holder AL, Hill SA, *et al.*, Determinants of anti-vascular action by combretastatin A-4 phosphate: role of nitric oxide. *Brit J Cancer* 2000; 83: 811-816 and Davis et al. Enhancement of vascular targeting by inhibitors of nitric oxide synthase. *Int J Radiat Oncol Biol Phys.* 2002; 54:1532-6). The following experiments show the surprising activity of the compound of Example 2 ((*Z*)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate).

Induction of Early Necrosis in SaS

The antitumour activity of vascular targeting agents is manifested as an early induction of tumour necrosis. SaS-bearing mice (tumour mean geometric diameter around 6mm) were treated i.p.with combretastatin A4 phosphate, the compound of Example 2 or no drug (controls) and tumors excised 24 h later. After fixation in formalin, sections were made from paraffin-embedded tumors and stained with hematoxylin and eosin. Sections were scored under the microscope in a blinded fashion according to the following scale: 0-10% necrosis = 1, 11-20% necrosis = 2, and so on until 91-100% necrosis =10. Results are mean scores of sections from at least three tumours. In this assay combretastatin A4 phosphate had little or no activity but the compound of Example 2, even when administered at a lower dose, had marked activity (Table 1).

Table 1. Induction of Necrosis in the SaS tumour

| Drug (dose) | Mean Necrosis Score±SEM |
|---|---|
| | |
| Control | 1.0 ± 0.0 |
| CA4P (500mg/kg) | 1.3 ± 0.2 |
| Compound of Example 2 (300mg/kg) | 7.2 ± 0.2 |

Growth Delay

Tumor growth was measured following i.p. dose administration. Tumor dimensions were measured in 3 orthogonal diameters using calipers. Five mice were included per treatment group. Growth delay was determined by the time taken to grow to 9 mm (geometric mean diameter, approximately 3mm diameter increase from starting diameter) minus the time for controls to do the same. In this assay combretastatin A4 phosphate (150mg/kg, i.p.) induced growth delay of 0.0 days whereas the compound of Example 2 (150mg/kg, i.p.) induced growth delay of 3.0days.

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